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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/827,294	04/20/2004	Akira Kubo	0283-0192PUS1	2590

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EXAMINER	
RAO, DEEPAK R	

ART UNIT	PAPER NUMBER
1624	

NOTIFICATION DATE	DELIVERY MODE
03/05/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/827,294	KUBO ET AL.	
	Examiner	Art Unit	
	Deepak Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16 and 19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-16* is/are allowed.

6)☒ Claim(s) *19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to the amendment filed on November 28, 2007.

Claims 1-16 and 19 are pending in this application.

Withdrawn Rejections/Objections:

Applicant is notified that any outstanding rejection/objection that is not expressly maintained in this office action has been withdrawn or rendered moot in view of applicant's amendments and/or remarks.

The following rejections are maintained:

Claim 19 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treatment for rheumatoid arthritis, osteoarthritis, gouty arthritis, synovitis, ulcerative colitis, Crohn's disease, etc., does not reasonably provide enablement for a method of treatment of malignant tumor, multiple sclerosis, acquired immunodeficiency syndrome, rejection and graft-versus-host diseases by organ transplantation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The reasons provided in the previous office action are incorporated here by reference.

Applicant's arguments have been fully considered but they were not deemed to be persuasive. Applicant relies on the references (Exhibits 1-38) and argues that 'the references demonstrate that the instant claim is enabled'. However, it is maintained that the state of the art does not establish the use of the claimed compounds in all of the assorted diverse methods of the

instant claims. For example, Suganuma cited to demonstrate enablement for malignant tumor, provides that 'In this study, we present the first evidence that tumor promotion by okadaic acid and TPA is critically dependent on TNF-α' (see page 4516). The reference, however, further provides that: "Whether okadaic acid or TPA would induce tumor promotion in mice deficient in both TNF-α and IL-1α or IL-1β remains to be investigated" (see page 4518). The instant claim recites 'a method of treatment of malignant tumor generally' and the reference establishes the unpredictability related to such therapeutic activity.

The instant claim includes 'a method for the treatment of multiple sclerosis'. The state of the art reference provided to show support for the instant claims does not seem to establish the claimed method. See Baker et al. (Exhibit 28) wherein it is stated that: "The precise mode of action of TNF-specific immunotherapy requires further elucidation and the relative involvement of TNF-α and TNF-β in the neural tissue, during EAE and MS is currently unknown" (see page 2047). As can be seen from the above, the cited state of the art references individually or collectively fail to establish the use of the instantly claimed compounds in the claimed methods, without the burden of undue experimentation for one of ordinary skill in the art.

The instant claim also recites 'a method for the treatment of acquired immunodeficiency syndrome' and the reference relied upon to demonstrate the claimed therapeutic activity, Cohen et al. (Exhibit 34) indicates that: "Although p38 MAPK activation has also been implicated in signaling proinflammatory cytokine production in monocytes and macrophages, less is known about the role of p38 activation in lymphocytes" (see page 340). Further, the reference provides in the same page that: "Although p38 MAP kinase activation has been implicated in HIV-1 infection of macrophages, it is non known whether it is also required for HIV-1 infection of T

lymphocytes". Regarding allograft rejection, McKee et al. (Exhibit 37) states that: "the mechanism(s) by which TNF-α and LTα mediate allograft rejection remains incompletely understood" (see page 483).

As can be seen from the above, the cited state of the art references individually or collectively fail to establish the use of the instantly claimed compounds in the claimed methods, without the burden of undue experimentation for one of ordinary skill in the art. To date, there is no conclusive evidence to establish the claimed therapeutic activity generally for a single class of compounds.

The instant claim encompasses the administration of the claimed compounds in 'a method for treating' a variety of diseases, having diverse mechanisms and etiologies and the specification or the references relied upon to demonstrate the therapeutic activity, do not provide any guidance as to how the claimed compounds are actually used in the treatment all types of diseases based on the biological activity of the compounds provided in the specification. The specification offers no guidance other than an invitation to the skilled artisan to perform random trial and error experimentation to try to find if the compounds are suitable therapeutic agents for those diseases.

As clearly explained in the previous office action, the instant claim continues to encompass treatment of several types of diseases, including various types of diseases which can affect different organs and having different methods of inflammation or harm to the body, and different vulnerabilities. The development of the most efficacious strategy for the treatment of the claimed diseases is based on understanding the underlying mechanisms of each type of disease. Some of the recited diseases involve a multi-step, multi-mechanism process and many of the types of the diseases of the instant claims are not alike, in spite of some apparent universal

characteristics. For example, inflammation promotion phase involves multiple mechanisms and there is no existence of a single therapeutic approach. Therefore, it is maintained that applicants have not provided sufficient test assays or data to support the instantly claimed treatment or other activity commensurate in scope with the claims, as of the filing date of the application.

When the best efforts have failed to achieve a goal, it is reasonable for the PTO to require evidence that such a goal has been accomplished, *In re Ferens*, 163 USPQ 609. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ2nd 1001, 1006.

Applicant has not provided sufficient evidence that establishes that the disclosure would have enabled for one skilled in the art at the time of filing. Further, the state of the art does not identify a single class of compounds that can treat all types of diseases or possess the biological activity of the instant claims. Further, one skilled in the art of medicinal therapy recognizes that there are complex interactions between individual genetic, developmental state, sex, dietary, environmental, drug, and lifestyle factors that contribute to the carcinogenic process, making it even more challenging to have a single therapeutic agent for the treatment of diverse diseases. Rigorously planned and executed clinical trials, incorporating measurement of appropriate biomarkers and pharmacodynamic endpoints are critical for selecting the optimal dose and schedule. A detailed understanding of the molecular mode of action of the various cytokines, alongside the elucidation of the molecular pathology of individual diseases is required to identify disease types and individual patients that may benefit most from treatment. It is also important to construct a pharmacologic audit trail linking molecular biomarkers and pharmacokinetic and pharmacodynamic parameters to receptor response endpoints. Therefore, it is maintained that

applicants have not provided sufficient test assays or data to support the various methods commensurate in scope with the claims, as of the filing date of the application.

Allowable Subject Matter

Claims 1-16 are allowed. The references of record do not teach or fairly suggest the instantly claimed compounds.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Monday-Friday from 8:00am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Deepak Rao/
Primary Examiner
Art Unit 1624

March 3, 2008